American Journal of Hematology 59:288–294 (1998)

Occurrence of Hemophilia in the United States

J. Michael Soucie,* Bruce Evatt, Debra Jackson, and the Hemophilia Surveillance System Project Investigators

National Center for Infectious Diseases, Hematologic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

An active surveillance system was used to identify all residents with hemophilia in six U.S. states (Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma). A hemophilia case was defined as a person with physician-diagnosed hemophilia A or B and/or a measured baseline factor VIII or IX activity (FA) of 30% or less. Case-finding methods included patient reports from physicians, clinical laboratories, hospitals, and hemophilia treatment centers. Once identified, trained data abstractors collected clinical and outcome data retrospectively from medical records. Among cases identified in 1993–1995, 2,743 were residents of the six states in 1994, of whom 2,156 (79%) had hemophilia A. Of those with available FA measurements, 1,140 (43%) had severe (FA < 1%), 684 (26%) had moderate (FA 1%–5%), and 848 (31%) had mild (FA 6%–30%) disease. The mean and median age was 25.4 and 23 years, respectively. The age-adjusted prevalence of hemophilia in all six states in 1994 was 13.4 cases/100,000 males (10.5 for hemophilia A and 2.9 for B). The prevalence by race/ethnicity was 13.2 cases/100,000 among white, 11.0 among African American, and 11.5 among Hispanic males. Application of age-specific prevalence rates from the six surveillance states to the U.S. population resulted in an estimated national population of 13,320 cases of hemophilia A and 3,640 cases of hemophilia B. For the 10-year period 1982–1991, the average incidence of hemophilia A and B in the hemophilia surveillance system (HSS) states was estimated to be 1 in 5,032 live male births. Am. J. Hematol. 59:288–294, 1998. Published 1998 Wiley-Liss, Inc.†

Key words: hemophilia; haemophilia; bleeding disorder; hematology; surveillance; public health; prevalence; incidence; epidemiology

INTRODUCTION

The congenital bleeding disorders hemophilia A and B are estimated to affect between 1 in 10,000 [1] and 1 in 5,000 [2] males. The complications of hemophilia, including severe, debilitating chronic joint disease and infectious diseases transmitted through blood products, create large demands on health care resources. However, little is known about the size and distribution of the United States hemophilia population and even less is known about the rate of complications from the disease or its treatment.

In 1975, the federal government established comprehensive hemophilia treatment centers (HTCs) to provide access to specialized treatment for persons with bleeding disorders [3]. Subsequently, the Centers for Disease Control and Prevention (CDC) developed prevention programs implemented through HTCs to reduce the complications of these disorders. In 1996, an estimated 13,000 persons with hemophilia A or B received care in one of the 139 federally supported HTCs located throughout the United States [4]. Although it is believed that about 60%–70% of the hemophilia population receives care in these centers, no data are available to confirm this.

Lack of health-care data has been a significant impediment to health planning efforts for persons with hemophilia and other bleeding disorders. Specifically, data are

The Hemophilia Surveillance System comprises the following persons and institutions: Centers for Disease Control and Prevention (B. Cicatello, B. Evatt, M.D., D. Jackson, F. Rickles, M.D., J.M. Soucie, Ph.D.); Colorado Department of Health (R. Hoffman, M.D., S. Michael, R.N., F. Nocera); Mountain States Regional Hemophilia Center (M. Manco-Johnson, M.D., R. Nuss, M.D., B. Riske, R.N., M.S.N, M.B.A., J. Stultz, M.P.H.); Georgia Division of Public Health (N. Stroup, Ph.D.); Emory University School of Public Health (E. Brockman, M.P.H., H. Hill, M.D., Ph.D., B. McDowell, T. Poindexter, M.P.H., K. Smith, M.P.H., S. Stein, M.D.); Louisiana State Department of Health (C. Myers); Louisiana Comprehensive Hemophilia Care Center (A. Abdou, M.P.H., B. Bates, M.P.H., J. Bunting, M.P.H., C. Leissinger, M.D., V. Shea, R.N., K. Wulff, R.N.); Massachusetts Department of Public Health (L. Livens, J. Su, D. Walker, Ed.D., N. Wilber, Ed.D.); Boston Hemophilia Center (B. Ewenstein, M.D., Ph.D., F. Ross); New England Hemophilia Center (D. Brettler, M.D., A. Forsberg, M.A., M.P.H., P. Geary, L.S.W., D. Thibeault); New York State Department of Health (M. Arrington, J. Bartholomew, B.S.N., R.N., B. Connelly, L.P.N., B. Cushman, R.N., B. Kearney, R.N., M. Kolakoski, M.S., J. Lima, J. Linden, M.D., M.P.H.); Mt. Sinai Medical Center (E. Aulov, S. Gaynor, R.N., M.B.A., Dr.P.H.); Oklahoma State Department of Health (S. Kinney, R.N., M.S.); Oklahoma Hemophilia Treatment Center (H. Huszti, Ph.D., F. Kiplinger, C. Sexauer, M.D.); and University of Oklahoma Health Sciences Center (N. Asal, Ph.D., L. Cowan, Ph.D., B. Erickson, M.P.H., L. Hudson, Ph.D., C. Smith-Edwards, M.A., S. Warner, M. Young).

*Correspondence to: J. Michael Soucie, Ph.D., NCID/DASTLR/HDB, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E64, Atlanta, GA 30333. E-mail: jps9@cdc.gov

Received for publication 6 April 1998; Accepted 12 August 1998

needed to: 1. Characterize the size and distribution of the population; 2. Measure rates of complications and health-care resource use; 3. Identify groups at high risk for complications; 4. Plan and prioritize local health preventive care strategies; 5. Disseminate accurate information to the community; and 6. Measure the impact of prevention programs and justify their continued support.

This article describes a surveillance system developed by CDC to identify all persons with hemophilia, including those not served by HTCs, in several U.S. states and to collect demographic, clinical, and medical resource utilization data. Data from the first three years of surveillance were used to estimate occurrence rates and describe the demographic characteristics of the hemophilia population in these states.

MATERIALS AND METHODS

We established an active surveillance system to identify cases and abstract data retrospectively from medical records. States were selected to participate based on a request for applications and an objective review process. The six states that comprise the hemophilia surveillance system (HSS), Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma, were estimated to include approximately 20 percent of the U.S. hemophilia population.

The system operates through state health departments to provide legal authority to identify patients and review medical records. Each health department works collaboratively with CDC and with established HTCs in the state to support specific key project personnel including a principal investigator, a project coordinator, and data abstractors. Project staff were trained by CDC and a detailed procedures manual was used in all data operations.

Hemophilia Case Finding

A definitive hemophilia case was defined as a person with physician-diagnosed hemophilia A or B and a baseline clotting factor activity level of $\leq$ 30%. A presumptive hemophilia case was defined as a person with either a physician diagnosis of hemophilia A or B or a measured factor VIII or IX activity level of $\leq$ 30%. Persons with acquired inhibitors of factor VIII or IX and carriers of the hemophilia gene were excluded. Severity level was categorized as mild if the activity level was 6%–30%, moderate if 1%–5%, and severe if < 1% of normal.

Surveillance staff in each state implemented methods of case finding that were best suited to the unique characteristics and data availability of that state. Staff in all six states used information obtained from a combination of disease-specific and general medical-care resources. A list of some of the resources used by staff in all states is presented in Table I. Methods implemented to protect patient confidentiality included lock-and-key protection of all patient data abstracts and assignment of a computer-generated identification code to all data contained in computerized databases.

TABLE I. Methods of Hemophilia Case Identification in Six U.S. States*

Disease-specific sources of care and support:
1. Hemophilia treatment centers
2. Regional hemophilia organizations
3. Patient advocacy groups
Other sources of care:
1. Hematologists, infectious disease specialists, and other physicians
2. Clinical laboratories that perform tests for clotting disorders
Material suppliers:
1. Clotting factor suppliers and distributors
2. Home health-care organizations
3. Pharmacies
4. Blood banks
Existing databases:
1. Hospital discharge lists
2. Death certificate information
3. Medicaid claims data
4. HIV/AIDS registries

*HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

Data Collection

Data collection began in January 1995. Patient data from medical care received during 1993–1994, and, starting in 1996, from care received in 1995 were abstracted from medical and clinic records by abstractors using a standardized data collection form (available upon request). Because cases were identified primarily through contacts with the medical care system and some cases did not have a medical care visit in every year, cases identified at any time during the three-year interval were eligible for inclusion in the system. However, because we wanted to estimate the prevalence of hemophilia in 1994, cases among persons who died in 1993 or who were born in 1995 were excluded from the analyses.

Detailed information was collected on: 1. Demographic and clinical characteristics; 2. The primary source of hemophilia care and reimbursement; 3. The number of bleeding episodes experienced; 4. The amount and sources of clotting factor used; 5. The results of testing for exposure to infectious diseases; 6. Results from comprehensive assessments of joints; and 7. All hospitalizations including admission and discharge diagnoses and length of stay. For patients infected with the human immunodeficiency virus (HIV), clinical data, such as CD4 counts and occurrences of AIDS-defining illnesses, were also collected. Finally, available data about the immediate and underlying causes of death were collected on patients who died during the three-year period. Since patients often received care in more than one setting during a calendar year, information from all medi-

cal care encounters during the year was aggregated prior to entry into a computerized database.

Statistical Analysis

Differences in the distribution of clinical characteristics among cases in the six states were assessed for statistical significance using chi-square tests. Rates were calculated only for men because few hemophilia cases were identified among women. For each state, the prevalence of hemophilia in 1994 was the number of identified definitive and presumptive hemophilia cases residing in the state in 1994 divided by the estimated state male population in 1994 and multiplied by 100,000 (cases per 100,000 males). State- and race-specific prevalence estimates were adjusted for age by direct standardization to the age distribution (five-year intervals; 0–4, 5–9, ... , 85+) of males in all six states [5]. Estimates of the total number of U.S. hemophilia cases were calculated by applying the age-specific prevalence rates in all six states to the estimated U.S. male population in 1994 for each corresponding age interval [6].

To estimate incidence, the number of prevalent cases in 1994 in all six states in persons with birth dates in each of the years 1982–1991 was used as the numerator and the number of live male births in all states for each year was used as the denominator [7]. We assumed that the population of the six states was steady, i.e., the number of people moving into the state was equal to the number leaving the state in any given year. Also, because incidence is underestimated by prevalence if mortality is not considered [8], we added to each numerator the number of persons with hemophilia in each birth cohort who died in the interval 1982–1994 according to the National Death Index [9]. For deaths occurring in 1993–1994, we added to birth cohort numerators only those deaths not already identified by the surveillance system.

RESULTS

Among males in the six states, a total of 2,628 hemophilia cases were identified in 1993, 2,684 cases in 1994, and 2,716 cases in 1995. In all, 3,029 unique cases were identified during the three-year period. Of these, 286 cases were excluded: 80 cases who died in 1993, 50 cases who were born in 1995, and 156 cases newly identified in 1995 whose state of residence in 1994 could not be documented. The remaining 2,743 cases were residents of the six surveillance states in 1994 and formed the study group. The mean (±SD) age of all cases was 25.4 (±18.4) years, and half of the population was younger than 23 years of age. Compared with the overall U.S. male population, the hemophilia population had a much greater proportion of males younger than 25 years (Fig. 1).

Of the 2,743 cases, 2,156 (79%) had hemophilia A (Table II). The proportion of cases with hemophilia A

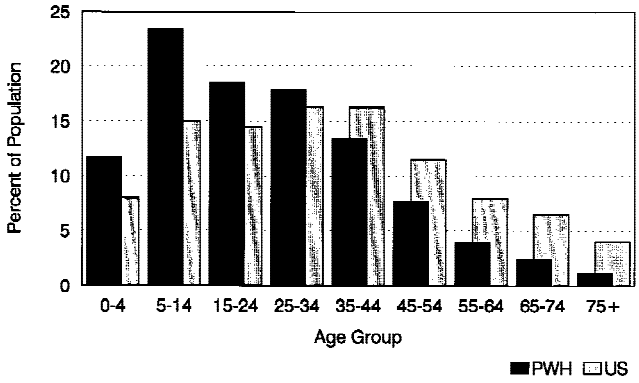

Fig. 1. Distribution by age of the male population for persons with hemophilia (PWH) and for residents of the United States (US) in 1994.

varied widely between states; from 71% in Louisiana to 84% in Massachusetts ($P = 0.001$). Among the 2,672 cases with known severity level, 1,140 (43%) had severe, 684 (25%) had moderate, and 848 (32%) had mild disease (Table II). Severity levels also varied substantially between states ($P < 0.001$) and the most extreme differences were seen in the proportion of cases with moderate disease, ranging from 13% in Massachusetts to nearly 35% in Georgia.

The age-adjusted prevalence of hemophilia in all six states in 1994 was 13.4 cases per 100,000 males (10.5 for hemophilia A and 2.9 for B) and ranged from 12.8 in Colorado to 13.7 in New York (Table II). The prevalence of hemophilia was highest for males 5–14 years of age (20.9 cases per 100,000 males) and declined steadily with increasing age to a low of 3.9 cases per 100,000 for males 75 years and older (Fig. 2). When examined by disease severity, the age-related rate of decline in prevalence occurred at a faster rate among severe compared with nonsevere cases beginning with the 25–34 year age group (Fig. 2). Application of age-specific prevalence rates from HSS states to the U.S. population resulted in an estimated national population in 1994 of 13,320 cases of hemophilia A and 3,640 cases of hemophilia B.

The distribution of hemophilia cases by race/ethnicity is shown in Table III. The age-adjusted prevalence of hemophilia per 100,000 population was 13.2 cases among white, 11.0 among African American, and 11.5 among Hispanic males. Other races represented among the cases included Native Americans, Asian/Pacific Islanders, and persons of mixed race. None of these groups included more than 1% of all cases. There were significant variations in the distribution of factor deficiency type ($P < 0.001$) and hemophilia severity ($P < 0.001$) across racial/ethnic groups.

Most hemophilia cases (92%) were identified through contact with a medical-care provider. Of such cases, 73% had visited an HTC at least once during the three-year period. Other medical-care sources included private phy-

TABLE II. Distribution of 2,743 Male Hemophilia Cases by State of Residence, Hemophilia Type, and Severity, 1994

					Hemophilia A + B[a]							
	Hemophilia A		Hemophilia B		Severe		Moderate		Mild			
State	N	%	N	%	N	%	N	%	N	%	Total	Prevalence[b]
Colorado	183	78.2	51	21.8	86	36.8	62	26.4	86	36.8	234	12.8
Georgia	394	82.2	85	17.8	175	38.6	157	34.6	122	26.8	479	13.6
Louisiana	196	71.3	79	28.7	136	50.2	51	18.8	84	31.0	275	12.9
Massachusetts	309	84.0	59	16.0	183	51.4	47	13.2	126	35.4	368	13.0
New York	916	77.4	267	22.6	483	41.6	328	28.2	350	30.2	1,181	13.7
Oklahoma	158	76.7	48	23.3	77	39.3	39	19.9	80	40.8	206	13.0
All 6 States	2,156	78.5	589	21.5	1,140	42.7	684	25.6	848	31.7	2,743	13.4

[a]Does not sum to total because of missing data.
[b]Cases per 100,000 population age-adjusted by direct standardization to the age distribution of all six states.

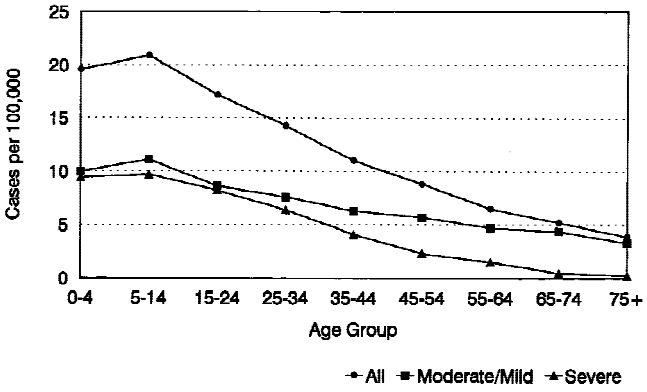

Fig. 2. The age-specific prevalence of hemophilia A and B in six U.S. states in 1994 according to severity level. Severity was assessed by factor activity and categorized as severe if < 1% and moderate/mild if 1%—30% of normal.

sicians or hematologists (13%) and hospital and nonhospital based clinics (4%); 8% of cases received care only in hospitals or emergency rooms. Overall, 1,834 (67%) of all identified hemophilia cases received care at an HTC during the study period and the proportion of cases with severe hemophilia was higher among HTC users vs. nonusers (53% vs. 17%, $P < 0.001$).

The incidence of hemophilia during the 10-year period from 1982–1991 (as estimated from prevalent cases in 1994) ranged from 1 in 5,650 live male births in 1986 to 1 in 4,574 live male births in 1987. The mean incidence over the period was 1 in 5,032 live male births. As expected, very few deaths occurred among these very young cohorts; no deaths among these cases were identified during the three years of active surveillance by HSS. Based on this incidence rate, an estimated 400 male infants with hemophilia are born in this country every year.

DISCUSSION

This is the first population-based study designed to measure the occurrence of hemophilia in this country. We found that the age-adjusted prevalence of hemophilia in six U.S. states in 1994 was 13.4 cases per 100,000 males. Four of five cases had hemophilia A, and 43% of all cases had severe disease. Prevalence rates were highest among 5–14 year olds and declined with age at a faster rate for severe compared with nonsevere cases. White, African-American, and Hispanic males were affected at similar rates and hemophilia incidence was estimated to be 1 in 5,032 male births.

In 1980, a comprehensive survey of the Swedish population found 564 hemophilia cases, a prevalence in that country of 13.7 cases per 100,000 males [10]. Geographic variations in prevalence rates and disease severity similar to those observed in HSS were also found in Sweden. Factors that may have contributed to the geographic differences in the present study include variations in the completeness of case finding and disparate diagnostic methodologies stemming from a lack of standardized laboratory testing. It is possible that large kindreds living in the same locale may also have played a role. Prevalence rates reported in other countries, based primarily on cases identified through contact with specialized hemophilia treatment centers, range from 9.7 to 20.5 cases per 100,000 males [11–15].

The lower prevalence observed in the youngest age group (1–4 years) compared with 5–14 year olds most likely reflects delay in diagnosis of milder cases. Nonetheless, younger age groups are over-represented in the hemophilia population, resulting in a median age of nearly 10 years less than that of the general male population. Lack of effective treatment in the past doubtless resulted in excess mortality among the oldest generations of cases, particularly those with severe disease. In addition, middle and older generations of cases were likely reduced by the epidemic of AIDS and hepatitis introduced into the population through use of plasma-derived factor concentrates [16,17]. The initial gains in longevity made possible by the availability of these factor-replacement products were counteracted by increased death rates from infectious diseases transmitted by these

TABLE III. Distribution of 2,743 Male Hemophilia Cases by Race/Ethnicity, Hemophilia Type, and Severity, 1994

	Hemophilia A		Hemophilia B		Hemophilia A + B[a]							
					Severe		Moderate		Mild			
State	N	%	N	%	N	%	N	%	N	%	Total	Prevalence[b]
White	1,565	79.0	416	21.0	819	42.4	483	25.0	629	32.6	1,980	13.2
African American	274	72.9	102	27.1	180	48.9	105	28.5	83	22.6	376	11.0
Hispanic	172	86.9	26	13.1	81	42.0	49	25.4	63	32.6	197	11.5
Other	145	76.3	45	23.7	60	33.3	47	26.1	73	40.6	190	—

[a]Does not sum to total because of missing data.
[b]Cases per 100,000 population age-adjusted by direct standardization to the age distribution of all six states.

TABLE IV. Incidence of Hemophilia A and B in HSS States, 1982–1991, Estimated From 1994 Prevalent Cases*

Birth cohort (year of birth)	1994 Prevalent cases	Deaths in birth cohort 1982–1994	Total male births in HSS states	Hemophilia incidence	
				Cases/100,000	Cases/births ratio
1991	68	0	339,547	20.0	1:4,993
1990	73	0	345,897	21.1	1:4,738
1989	66	1	341,754	19.6	1:5,101
1988	67	1	332,330	20.5	1:4,887
1987	71	0	324,733	21.9	1:4,574
1986	56	1	322,070	17.7	1:5,650
1985	66	0	321,553	20.5	1:4,872
1984	58	0	312,987	18.5	1:5,396
1983	57	2	311,800	18.9	1:5,285
1982	62	3	313,301	20.8	1:4,820

*HSS, hemophilia surveillance system. HSS states include Colorado, Georgia, Louisiana, Massachusetts, New York, and Oklahoma.

products prior to the incorporation in 1985 of viral inactivation procedures [18].

In the United States, studies of persons with hemophilia that specify race refer to the small proportion of minorities represented among cases. Although the numbers of cases among African-American and Hispanic males in the six surveillance states were one-fifth and one-tenth the number among whites, respectively, and 72% of all identified cases were white, rates of hemophilia among these race groups were similar when age-distribution and population size differences were considered.

We are unaware of published rates of hemophilia among Native Americans. In Oklahoma, one of the states covered by the surveillance, Native Americans comprise 8% of the total population. Extensive case-finding efforts in this population identified 15 cases, representing 7% of all identified hemophilia cases in that state. The resultant prevalence rate of 12.2 per 100,000 Native American males is similar to rates among the other race groups.

The incidence of hemophilia among Chinese persons has been reported to be about one-fourth of that among whites [19]. Only 22 cases among persons of Asian or Pacific Islander descent were identified in all six states, resulting in a prevalence of hemophilia in this group of 4.3 per 100,000 Asian/Pacific Islander males. While this rate is lower than that found among other racial/ethnic groups, these results should be interpreted with caution. Rates in this population varied considerably between states, ranging from 0 to 15.3 per 100,000 males. Although some of the variability in rates was probably due to the magnified effect of small differences between states in the numbers of cases found, there may also have been true differences in case finding between states. Moreover, the diversity of races that are included in the classification of Asian or Pacific Islander further complicates the interpretation of these findings.

Overall, 67% of the hemophilia population visited an HTC at least once during the three-year study period. These centers were established with support from the federal government to offer specialized care to persons with bleeding disorders. Studies have reported improved health, decreased hospitalization and unemployment rates, and decreased cost of care among persons with hemophilia after establishment of these centers [20]. In Canada, annual comprehensive care administered by similar centers has been incorporated into clinical practice guidelines for hemophilia [21]. Our finding that cases among persons who were treated at HTCs were more likely to have severe disease is not surprising and suggests appropriate use of HTCs by persons who can benefit most from the services provided. Nonetheless,

about 14% of severe and 34% of moderate cases had no contact with an HTC during the three-year study period, suggesting that these centers may be underutilized.

The estimated incidence of hemophilia based on the prevalent population in the six HSS states was higher than some previously reported rates. The widely cited incidence estimate of 1 in 10,000 males appears to have origins in studies during the 1960s. Results from the first study, published in 1962, estimated an incidence of ''at least 1 in 10,000'' on the basis of 150 cases identified in Pittsburgh [22]. The results of two later studies that combined limited population data with estimates of mutation rates supported this rate [23,24]. More recently, hemophilia incidence has been cited as 1 in 5,000 male births, apparently based on a report by Rosendaal and Briet [2] who proposed that the highest age-specific prevalence rate observed in a survey of Danish hemophiliacs represented the closest estimate of ''prevalence at birth.'' Even though this estimate did not consider mortality, our results support this finding. The highest age-specific prevalence in our study was 20.9 cases per 100,000 5–14 year-old males, a rate nearly identical to the 20.6 cases per 100,000 15–34 year-old males reported by Rosendaal and Briet [2]. Even after taking mortality into account, incidence rates averaged very nearly 1 in 5,000 male births over a 10-year period. This similarity between incidence estimates that do and do not account for deaths is a result of low mortality rates in the youngest cohorts.

Several limitations should be considered when interpreting the results of this study. First, we included 71 (2.6%) presumptive cases in our analyses that may have led to overestimates of occurrence. Persons with physician-diagnosed hemophilia who did not have measured factor activity may have had levels higher than the 30% upper limit required for inclusion in the study. However, in the absence of these measures, diagnosis must have been made on the basis of symptoms that become much less likely as factor activity levels rise above this level. Additionally, because the presumptive cases were equally distributed throughout states and across race groups (results not shown), their inclusion was unlikely to have differentially affected state- and race-specific rates.

Among cases identified in 1995, 156 were excluded because their 1994 state of residence could not be verified. Thus, prevalence may have been underestimated—perhaps as much as 5% if all 156 cases had in fact been residents of the surveillance states in 1994. In addition, cases identified through contact with the medical care system were more likely to have severe disease because of the increased need for primary or secondary care of bleeding-related complications. We attempted to minimize the undercount of mild cases in two ways. First, by identifying cases over a three-year period, infrequent medical care users were more likely to be captured. Second, all surveillance sites used a variety of case-finding methods including, in one state, the designation of hemophilia as a reportable condition. Overall, about 8% of cases had no known contact with the medical care system during the three-year period, 53% of whom had mild disease compared with 29% among medical care users. The similarity of prevalence rates among the six states despite differences in case-finding methodologies and an overall prevalence rate comparable to that found in countries with registries provides evidence for complete case ascertainment by the HSS. However, because some cases may have gone undetected, actual occurrence rates of hemophilia may be higher than those we report.

Over the past 20 years, great strides have been made in the development of therapeutic technologies to treat hemophilia. However, efforts to assess the impact of these new technologies have been hampered by the lack of population-based information about the sources and outcomes of care of persons with hemophilia. The HSS was developed to provide CDC and other public health agencies with information critical to continued efforts to reduce or prevent the complications of this condition.

REFERENCES

1. Merritt AD, Conneally PM. Hemophilia: Genetics and counseling. In Hilgartner MW, ed. Hemophilia in Children. Littleton, MA: Publishing Sciences Group, Inc., 1976.
2. Rosendaal FR, Briet E: The increasing prevalence of haemophilia. Thromb Haemostasis 63:145, 1990.
3. PL 9463: The Public Health Service Act establishing the hemophilia diagnostic and treatment center program. No. 1131 of Public Law 9463. Washington, DC: Government Printing Office, 1975.
4. National Center for Infectious Diseases, Hematologic Diseases Branch: 1996 Hemophilia minimal data set for risk reduction. Atlanta: Centers for Disease Control and Prevention, 1997.
5. Rothman KJ: Modern Epidemiology. Boston: Little, Brown, and Company, 1986, p 41.
6. Byerly ER, Deardorff K: National and state population estimates: 1990 to 1994. U.S. Bureau of the Census. Current population reports, P25-1127. Washington, DC: U.S. Government Printing Office, 1995.
7. National Center for Health Statistics: Vital statistics of the United States, 1992, vol I, natality. Washington, DC: Public Health Service, 1995.
8. Freeman J, Hutchison GB: Prevalence, incidence and duration. Am J Epidemiol 112:707, 1980.
9. U.S. Department of Health and Human Services: Vital statistics mortality data, multiple cause detail, 1979–1995. Public use data tape contents and documentation package. Hyattsville, MD: Centers for Disease Control and Prevention, National Center for Health Statistics, 1997.
10. Larsson SA, Nilsson IM, Blomback M: Current status of Swedish hemophiliacs. I. A demographic survey. Acta Med Scand 212:195, 1982.
11. Rosendaal FR, Varekamp I, Smit C, Brocker-Vriends AHJT, van Dijck H, Vandenbroucke JP, Hermans J, Suurmeijer TPBM, Briet E: Mortality and causes of death in Dutch haemophiliacs, 1973–86. Br J Haematol 71:71, 1989.
12. Walker I: Survey of the Canadian hemophilia population. Can J Public Health 82:127, 1991.

13. Rizza CR, Spooner RJD: Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976–80: Report on behalf of the directors of haemophilia centres in the United Kingdom. Br Med J 286:929, 1983.
14. Koumbarelis E, Rosendaal FR, Gialeraki A, Karafoulidou A, Noteboom WMP, Loizou C, Panayotopoulou C, Markakis C, Mandalaki T: Epidemiology of haemophilia in Greece: An overview. Thromb Haemostasis 72:808, 1994.
15. Ghirardini A, Schinaia N, Chiarotti F, De Biasi R, Rodeghiero F, Binkin N, and the GICC: Epidemiology of hemophilia and of HIV infection in Italy. J Clin Epidemiol 47:1297, 1994.
16. Eyster ME, Schaefer JH, Ragni MV, Gorenc TJ, Shapiro S, Cutter S, Kajani MK, Abrams J, Barron LE, Odenwelder A, Lusch C, Brennan M, DeGreen HP, Phillips L, Cohen AR, Butler RB: Changing causes of death in Pennsylvania's hemophiliacs 1976–1991: Impact of liver disease and acquired immunodeficiency syndrome. Blood 79:2494, 1992.
17. Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E: Mortality in patients with hemophilia: Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. Ann Intern Med 123:823, 1995.
18. Chorba TL, Holman RC, Strine TW, Clarke MJ, Evatt BL: Changes in longevity and causes of death among persons with hemophilia A. Am J Hematol 45:112, 1994.
19. Chan V, Chan TK, Liu VWS, Wong ACK: Restriction fragment length polymorphisms associated with factor VIII:C gene in Chinese. Hum Genet 79:128, 1988.
20. Smith PS, Levine PH: The benefits of comprehensive care for hemophilia: A five-year study of outcomes. Am J Public Health 74:616, 1984.
21. Association of Hemophilia Clinic Directors of Canada: Hemophilia and von Willebrand's disease: 1. Diagnosis, comprehensive care and assessment (Clinical Practice Guidelines). Can Med Assoc J 153:19, 1995.
22. Lewis JH, Didisheim P, Ferguson JH, Li CC: Genetic considerations in familial hemorrhagic disease. I. The sex-linked recessive disorders, hemophilia and PTC deficiency. Am J Hum Genet 15:53, 1963.
23. Stevenson AC, Kerr CB: On the distributions of frequencies of mutation to genes determining harmful traits in man. Mutat Res 4:339, 1967.
24. Barrai I, Cann HM, Cavalli-Sforza LL, de Nicola P: The effect of parental age on rates of mutation for hemophilia and evidence for differing mutation rates for hemophilia A and B. Am J Hum Genet 20:175, 1968.